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קשה לפטנט
Application for Patent

I (Name and address of applicant, and in case of body corporate-place of incorporati (שם המבקש, מענו ולגבי גוף מאוגד - מקום התאגדותו)

FARBENFABRIKEN BAYER
AKTIENGESELLSCHAFT, of 509 Leverkusei
Bayerwerk, Germany.

Owner, by virtue של אמצאה מכח הדין ..... of an invention the title of which is שמה הוא

(Hebrew) (עברית): תולדות 4-הידרוקסי פיפרידין והכנתן

(English) (אנגלית): 4-Hydroxy-piperidine derivatives and their preparation

hereby apply for a patent to be granted to me in respect thereof. :מבקש בזאת כי ינתן לי עליה פטנט

• בקשת חלוקה— Application of Division	• בקשת פטנט מוסף— Application for Patent of Addition
מבקשת פטנט from Application	• לבקשה/לפטנט to Patent / Appl.
No. ..... מס'	No. ..... מס'
dated ..... מיום	dated ..... מיום

• ייפוי כח : כללי / ~~מצורף — בזה / עד יוגש~~
P.O.A. : general / ~~individual — attached / to be filed later~~

filed in case ..... הוגש בענין קודם

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חתימת המבקש
Signature of Applicant

For the Applicants
DR. REINHOLD COHN AND PARTNERS
By:

• דרישה דין קדימה
Priority Claim

מדינת האגוד Convention Country	תאריך Date	מספר/סימן Number / Mark
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Tl of the year of

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תאריך

יפס זה, כשהוא מוטבע בחותם לשכת הפטנטים ומושלם במספר ובתאריך ההגשה, הנו אישור להגשת הבקשה שפרטיה רשומים לעיל.
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PATENTS AND DESIGNS ORDINANCE

SPECIFICATION

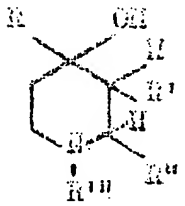
4-Hydroxy-piperidine derivatives and their preparation

נוגדות 4-הידרוקסי פיפריזין והכנתן

I (we) FARBENFABRIKEN BAYER AKTIENGESELLSCHAFT, a German company, of Leverkusen-Bayerwerk, Germany

do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:-

The present invention consists in derivatives of 4-hydroxy-piperidine of the formula:

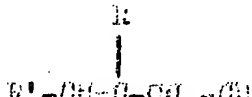


I

in which R is an alkyl, aryl or aralkyl radical, R' is hydrogen, a primary-linked alkyl, alkenyl or aralkyl radical or an aryl radical, R'' is hydrogen, an alkyl, aralkyl, aryl or pyridyl radical and R''' is hydrogen, an alkyl or aralkyl radical, the aryl or aralkyl rings are optionally substituted by alkyl, alkoxy, nitro or halogen, and the radicals R, R', R'' and R''' may be the same or different.

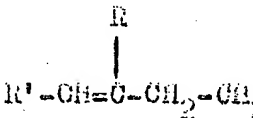
The invention also consists in processes for the preparation of compounds of formula I above.

In one process compounds of formula I in which R''' is hydrogen are prepared by the partial hydrogenation of a β,γ-unsaturated nitrile of the formula:



II

at the cyano group whereby a primary γ,δ-unsaturated amine of the formula:



IIIa

is formed and condensation of the latter in an acidic solution with an aldehyde R''.CHO, where R, R' and R'' have the same meanings as in formula I.

In a second process, compounds of formula I in which R''' is alkyl or aralkyl, are prepared by the hydrogenation of a nitrile of formula II above in the presence of an amine:

$R'''NH_2$

to form a secondary γ,δ-unsaturated amine of the formula:

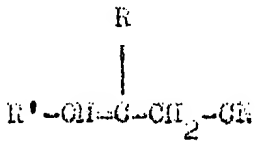
$$R'-CH=\overset{R}{\underset{|}{C}}-CH_2-CH_2NH-R''' \qquad \text{IIIb}$$

and condensation of the latter with an aldehyde R".CHO, where R, R' and R" have the same meaning as in formula I and R''' is as above.

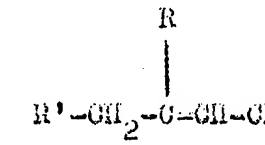
A condensation reaction of this type has been known only as a special case of the Pictet-Spengler

synthesis of tetrahydro-isoquinolines, which consists in the condensation of β-phenyl-ethylamines with aldehydes, i.e. condensation of tetrahydrophenyl-ethylamine (cyclohexenyl-ethylamine) with aldehydes to 10-hydroxy-decahydro-isoquinolines /Annalen, 561, 85; 583, 110 (1953)7. The fact that this known variant of the Pictet-Spengler synthesis can also be generally applied to open-chain γ,δ-unsaturated amines and thus represents only a special case of a synthesis now recognised as being generally applicable, was hitherto unknown.

The starting materials of the process according to the invention are β,γ-unsaturated nitriles of the formula II, such as are obtained, for example, by the condensation of ketones of the general constitution $R'.CH_2.CO.R$ with cyano-acetic acid. These nitriles may contain some amount of the isomeric α,β-unsaturated nitriles IV



II



IV

in which R and R' have the above meanings.

If R is alkyl or aralkyl, the β,γ-unsaturated nitrile of formula II can exist in two stereoisomeric forms.

The composition of these nitrile mixtures depends upon the substituents R and R'.

The α,β- and β,γ-unsaturated nitriles can also be obtained by other known methods, such as by substitution of the halogen in corresponding ω-halo-olefins by the

cyano group.

It is not necessary to separate the β,γ-unsaturated nitriles required as starting material in the process according to the invention from the α,β- and β,γ-unsaturated nitriles since only the former can be hydrogenated catalytically to form the γ,δ-unsaturated amines III. As described below, the hydrogenation of the admixed α,β-unsaturated nitriles yields products which do not interfere with the course of the further reaction.

The first step of the process according to the invention consists in the reduction of the cyano group of the β,γ-unsaturated nitriles whereby γ,δ-unsaturated amines are formed. This reduction is preferably carried out with catalytically activated hydrogen in alcoholic solution with a Raney catalyst, especially Raney nickel or Raney cobalt. Since only the cyano group is to be hydrogenated while the double bond shall subsist, it is expedient to work at room temperature or at an only slightly increased temperature, e.g., at 50 - 70°C. The precise conditions of the hydrogenation depend essentially on the activity of the catalyst, but the object of the invention is best achieved with catalyst of average activity. It is, therefore, recommended partially to de-activate highly active catalysts by usual methods, e.g., by the addition of ferrous sulphate. Suitable solvents for use in the reaction mixture are, for example, lower alcohols, such as methanol or ethanol; hydrocarbons such as benzene, toluene or cyclohexane; ethers such as tetrahydrofuran or dioxan; and the like. Where the amine

of formula III is to be a primary amine, it is expedient to use the usual additives to the reaction mixture, such as ammonia, ammonium acetate, or potassium hydroxide, in order to avoid the formation of secondary amines.

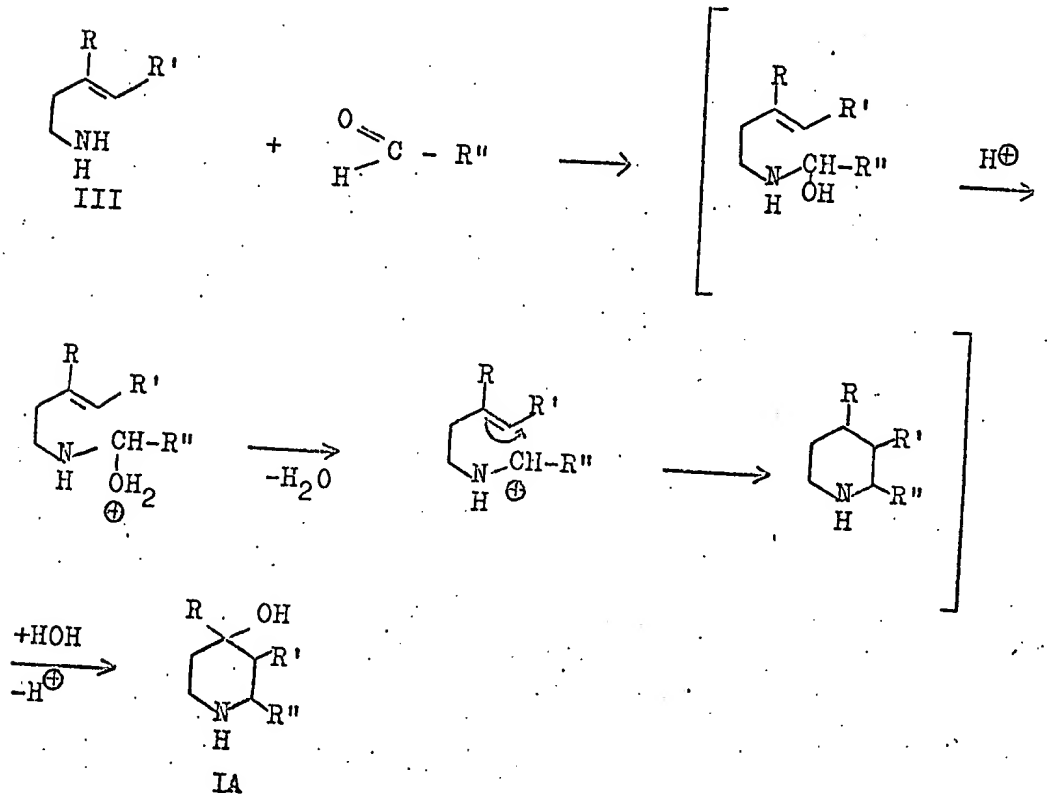
Instead of performing the reduction of the nitriles II or II + IV to the amines III by catalytic hydrogenation, any other suitable reductant may be used, such as nascent hydrogen, sodium in alcohol, alkali metal or alkaline earth metal alanates or borohydrides in the solvents or diluents usual for this purpose.

The product of the hydrogenation is a mixture of the desired γ,δ-unsaturated amine of formula III, and of saturated amines and possibly β,γ-unsaturated amines, both being hydrogenation products of the originally present α,β-unsaturated nitriles of formula IV. The relative proportions of γ,δ-unsaturated amines on the one hand, and saturated and β,γ-unsaturated amines on the other hand need not necessarily correspond to the relative proportions of the β,γ-nitriles and α,β-nitriles in the starting mixture of the hydrogenation since in the course of the reduction a displacement of the double bond is apt to occur under the influence of the reductant, e.g., lithium alanate.

Instead of the primary amines III in which R'", is hydrogen, the corresponding secondary amines in which R'" is alkyl or aralkyl, such as methyl, ethyl, benzyl, β-phenylethyl, and the like may serve as intermediates in the synthesis of the piperidines of formula I. These secondary amines III can be prepared by conventional methods. by one of them the nitriles II or II + IV, are

subjected to hydrogenation in the presence of primary amines $R'''.NH_2$.

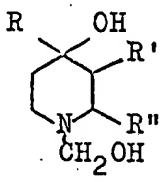
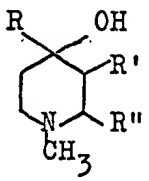
Another method for preparation of compounds of formula I subjects a primary amine of formula III to reaction with an aldehyde according to the following scheme:



If desired, the compound of formula IA which is a compound of formula I above in which R''' is hydrogen, may be subjected to alkylation or aralkylation, whereby a compound of the formula I above in which R''' is alkyl or aralkyl is obtained.

If in the method according to the above scheme formaldehyde is used as the aldehyde, and this in a great excess, the reaction proceeds first as indicated above but the compound of formula IA is at once converted to the corresponding N-hydroxymethyl compound. This, in turn, can be reduced,

without being isolated, with H_2/Ni to the corresponding N-methyl compound. The sequence of reactions is illustrated by the following scheme:

Compound IA + CH_2O ⟶  $\xrightarrow{H_2/Ni}$ 

B

The last step of the new synthesis according to the invention, the condensation of the amines (III) with aldehydes R".CHO to the 4-hydroxy-piperidine derivatives (I), is carried out in acidic aqueous solution at pH 2 - 4. The experimental conditions of this condensation can vary within wide limits; it is possible to work in a concentrated, about 10 - 30%, soluti or, as has generally proved to be advantageous, in an about 0.1 0.2 molar solution, corresponding to a concentration of amine of about 1 - 5%.

Normally the waterbath temperature is chosen as the reaction temperature, i.e. about 80 - 90° C.; with especially reactive aldehydes, such as formaldehyde, the condensation according to the invention can also be carried out at room temperature or at an only slightly increased temperature, e.g. at 30 - 50° C.

The aldehydes employed for the condensation are, in general, used in the free form. Alternatively, however, there can also be used as aldehyde equivalents those compounds which, under the reaction conditions, are gradually converted into the free aldehydes capable of condensation, such as para-formaldehyd as a source for formaldehyde; paraldehyde for acetaldehyde; or phenyl-glycid ic acid esters for phenylacetaldehyde; instead of the free aldehydes, their bisulphite compounds can also be used.

The duration of the reaction depends upon the condensa tion ability of the aldehydes used or the speed with which the

aldehydes are liberated from the equivalent forms used. If working at 80 - 90° C., then a complete reaction is already achieved with reactive aldehydes after heating for about 1 hour, but generally after heating for about 12 - 24 hours, where with aldehyde equivalent forms which slowly split off or with sterically hindered aldehydes, a prolonged heating e.g. for 2 - 6 days, may be necessary. When reactive formaldehyde is used, the condensation also takes place by standing for several weeks at room temperature.

As to the relative amount of aldehyde used, the condensation of primary γ,δ-unsaturated amines is carried out with the application of the calculated molar amount. If, however working with formaldehyde, and it is intended to convert the 4-hydroxy-piperidine derivative formed according to the invention into the corresponding N-methyl compound, then formaldehyde can also be used in excess since the N-methylol-4-hydroxy-piperidine derivative which is now formed can easily be reduced to the N-methyl compound.

The maintenance of the pH optimum of pH 2 - 4 is important for attaining maximum yields of 4-hydroxy-piperidines. If a greater excess of acid is used (pH~1), then an undesirable dehydration of the 4-hydroxy-piperidines to $\Delta^{3,4}$-piperidines may take place.

The 4-hydroxy-piperidine derivatives according to the invention are important intermediates in the synthesis of pharmacodynamically, highly active substances, e.g. analgesics of morphine-like action.

For example, the N-methyl-2-p-methoxybenzyl-3,4-dimethyl-4-hydroxy-piperidine can be converted into 2,5,9-trimethyl-2'-hydroxy-6,7-benzomorphane by boiling with constan boiling hydrobromic acid.

The N-3-dimethyl-4-p-phenyl-4-hydroxy-piperidine (in Example 9 below) can be converted into the corresponding 4-propionyloxy-derivative by treatment with propionic acid anhydride and pyridine. This derivative is known to have morphine-like analgetic properties.

The invention is illustrated by the following non-limitative examples.

EXAMPLE 1

2-p-methoxybenzyl-3,4-dimethyl-4-hydroxy-piperidine

(a) 285 g. (3 mol) of a mixture of 3-methyl-$\Delta^{2,3}$-pentenonitrile and 3-methyl-$\Delta^{3,4}$-pentenonitrile (obtained by the condensation of methyl ethyl ketone with cyanoacetic acid; b.p. 156 - 157° C.) are dissolved in 1 litre of methanol and, after the addition of 30 g. of Raney cobalt and 30 ml. of a 0. molar aqueous ferrous sulphate solution, hydrogenated at 50 - 70° C. and at a pressure of 50 atmospheres of hydrogen until termination of the hydrogen absorption, i.e. 139 litres of hyd within 1 hour. After cooling, the catalyst is separated, the solution acidified, while cooling, with 300 ml. of concentrate hydrochloric acid and the methanol evaporated from this soluti in a vacuum at 50° C. The base is liberated, with strong cool from the aqueous solution obtained, by means of a concentrated sodium hydroxide solution, the base is taken up with ether, th ether solution dried over potassium hydroxide and, after evaporation of the ether, the base is distilled:
b.p. 125 - 128° C.; yield 180 g. (60% of theory).

This reduction can also be carried out with lithium alanate:

A solution of 142.5 g. (1.5 mol) of a mixture of 3-methyl-$\Delta^{2,3}$-pentenonitrile and 3-methyl-$\Delta^{3,4}$-pentenonitrile (see above) in 100 ml. of anhydrous ether is added dropwise, with stirring, at -10 to -5° C. to 68.5 g. (1.8 mol) of lithium alan in 500 ml. of anhydrous ether. The reaction mixture is allowed to warm up slowly to room temperature, stirred at room temperatu for a further 12 hours and thereafter decomposed by the dropwise addition of a 20% sodium hydroxide solution. The ether layer is separated, the resultant base shaken out with 5% hydrochloric acid, the base liberated from the clear acidic solution with a concentrated sodium hydroxide solution and isolated with ether in the usual way: b.p. 130 - 132° C.

(b) 50 g. (0.5 mol) of the so obtained primary amine (mixture of 3-methyl-pentylamine and 3-methyl-$\Delta^{3,4}$-pentenyl-amine) are dissolved in 535 ml. of 1N hydrochloric acid, the solution diluted with 1965 ml. of water (pH≈3) and, after the addition of 104 g. (0.5 mol) of p-methoxy-phenyl-glycidic acid methyl ester, heated at 80 - 90° C. for 2 - 3 days, with vigorou stirring. After cooling, resin-like impurities are filtered off the solution is covered with a small amount of ether and the resultant base separated by the addition of a 50% potassium carbonate solution. After standing for several hours, the condensation product has separated in crystalline form at the interface between the organic and aqueous separating layer. The product is filtered off with suction and

washed with water and a little ice cold ether. In this manner there are obtained 26.5 g. of 2-p-methoxybenzyl-3,4-dimethyl-4-hydroxy-piperidine of m.p. 140 - 141° C.

$C_{15}H_{23}NO_3$ (249)

Calc. C 72.27 H 9.30 N 5.62 OCH_3 12.45

Found C 72.22 H 9.52 N 5.45 OCH_3 12.59

From the ethereal mother liquor of the first crystallization there is obtained, after distillation of the residue obtained by evaporation of the ether (b.p. 160 - 165° C./0.01 mm.Hg.), a rapidly solidifying oil; from ether, 3.5 g., m.p. 134 - 136° C., which is presumably a stereoisomer of the form first obtained.

$C_{15}H_{23}NO_3$ (249)

Calc. C 72.27 H 9.30 N 5.62

Found C 72.50 H 9.25 N 5.69

Total yield 30 g.; since the starting amine only contained about 50% 3-methyl-$\Delta^{3,4}$-pentenylamine, the yield amounts to about 50% of theory.

If the p-methoxyphenylglycide methyl ester is replaced by the equimolar amount of benzaldehyde and the procedure is otherwise the same as that described under (b), then there is obtained 2-phenyl-3,4-dimethyl-4-hydroxy-piperidine of m.p. 165 - 167° C.

$C_{13}H_{19}NO$ (205)

Calc.	C 76.04	H 9.33	N 6.82
Found	C 76.18	H 9.22	N 6.90

By replacing the benzaldehyde by the equimolar amount of freshly distilled isobutyraldehyde, there is obtained, analogously, 2-isopropyl-3,4-dimethyl-4-hydroxy-piperidine of m.p. 118 - 120° C.

$C_{10}H_{21}NO$ (171)

Calc.	C 70.11	H 12.36	N 8.18
Found	C 70.10	H 11.88	N 8.23

By replacing the p-methoxyphenylglycidic acid methyl ester with equimolar amounts of various aldehydes and proceeding in the remaining way as described under b), there are obtained, for example, the following compounds:

Aldehyde	Reaction Product	
4-Methoxybenzaldehyde	2-p-methoxyphenyl-3,4-dimethyl-4-hydroxy-piperidine	m.p. 144-146°C
3-Chlorobenzaldehyde	2-m-chlorophenyl-3,4-dimethyl-4-hydroxy-piperidine	m.p. 150-153°C
	2-m-chlorophenyl-3,4-dimethyl-4-hydroxy-piperidine (stereo-isomeric form)	m.p. 137-139°C
	2-m-chlorophenyl-3,4-dimethyl-4-hydroxy-piperidine (isomeric mixture)	B.p. $Kp_{0.15}$ 138-141°C

Aldehyde	Reaction Product	
3,4-Dimethoxybenzaldehyde	2-(3',4'-dimethoxyphenyl)-3,4-dimethyl-4-hydroxypiperidine	m.p. 132-135°
2-Nitrobenzaldehyde	2-o-nitrophenyl-3,4-dimethyl-4-hydroxypiperidine	m.p. 203-205°
4-Nitrobenzaldehyde	2-p-nitrophenyl-3,4-dimethyl-4-hydroxypiperidine	m.p. 168-171°
Pyridine-2-aldehyde	2-(2'-pyridyl)-3,4-dimethyl-4-hydroxypiperidine	m.p. 108-111°
Pyridine-4-aldehyde	2-(4'-pyridyl)-3,4-dimethyl-4-hydroxypiperidine	m.p. 146-148°

EXAMPLE 2

3-methyl-4-phenyl-4-hydroxy-piperidine

(a) 78.5 g. (0.5 mol) of 3-phenyl-$\Delta^{3,4}$-pentenonitril (prepared by the condensation of propiophenone with cyanoacetic acid; b.p. 115° C./7mm.Hg.; it exclusively contains the β,γ-unsaturated nitrile) are dissolved in 200 ml. of methanol and, after the addition of 10 g. of Raney cobalt and 10 ml. of 0.1 molar aqueous ferrous sulphate solution, are hydrogenated a 70° C. and at a pressure of 50 atmospheres of hydrogen until th absorption of hydrogen is completed, i.e. 19.7 litres of hydrog within 1 hour. After cooling, the catalyst is filtered off wit suction, the methanol evaporated from the solution in a vacuum and the residue distilled in a vacuum. Yield: 58.7 g. of 3-ph $\Delta^{3,4}$-pentenylamine (73% of theory) b.p. 96 - 98° C./9 mm.Hg.

(b) 80.5 g. (0.5 mol) of the 3-phenyl-$\Delta^{3,4}$-pentenylamine are dissolved in 545 ml. of 1N hydrochloric acid, diluted with 2000 ml. of water and, after the addition of 50 g. of a 30% formalin solution, stirred for 40 hours at 80 - 90° C. The pH of the solution is 3.0; its concentration is about 0.2 molar. After cooling, the reaction mixture is rendered alkaline by the addition of a concentrated sodium hydroxide solution, the separated oil is taken up in about 3 litres of ether, separated and washed with a concentrated sodium chloride solution. After concentration of the ether solution to about 500 ml., crystallization starts.

1st crystallizate: 23.8 g., m.p. 126 - 142° C.

From the mother liquor after further concentration:

2nd crystallizate: 13.0 g., m.p. 118 - 121° C.

Residual mother liquor evaporated, residue distilled:

(a) b.p. 95 - 120° C./9 mm.Hg.; 8.1 g. starting amin

(b) b.p. 135 - 140° C./1.4 mm.Hg.; 38.2 g.; solidifies to a soft, crystalline mass.

Total yield: 75 g., i.e. 87.5% of theory, referred to the reacted amine.

The crystallizates are mixtures of the α- and β-stereoisomers of 3-methyl-4-phenyl-4-hydroxy-piperidine, which can be separated by fractional crystallization from ether: α-compound: m.p. 125 - 126° C.; β-compound: m.p. 150 - 151° C

$C_{12}H_{17}NO$ (191); (m.p. 150-151°C.)

Calc. C 75.40 H 8.90 N 7.34

Found C 75.30 H 8.95 N 7.29

N-methyl derivative of the α-compound: m.p. 78 - 8

$C_{13}H_{19}NO$ (205)

Calc. C 76.05 H 9.33 N 6.82

Found C 76.15 H 9.36 N 7.08

When working is carried out in 1 molar solution by heating 16.1 g. (0.1 mol) of 3-phenyl-$\Delta^{3,4}$-pentenylamine, 16. ml. of 6.5 1N hydrochloric acid, 78 ml. of water and 11 g. o 30% formalin solution for about 50 hours, there are isolated:

(a) 4.2 g., m.p. 153° C.; β-3-methyl-4-phenyl-4-hydroxy-piperidine

(b) 8.2 g., b.p. 135° C./1.5 mm.Hg.; solidifies ether; mixture of the stereomers, besides 2. of starting amine.

Yield 75% of theory, referred to the reacted amine

When the same reaction mixture is heated for only hour, there are obtained:

(a) 2.8 g., m.p. 152 - 153° C.; β-compound

(b) b.p. 130° C./0.8 mm.Hg.; 11.2 g.; crystalli upon treatment with ether; in addition 2.3 g starting amine.

Yield 82.4% of theory, referred to the reacted ami

When an analogous 0.1 mol reaction mixture is allowe to stand for 39 days at room temperature in a 0.1 molar soluti (16.1 g. of 3-phenyl-$\Delta^{3,4}$-pentenylamine, 105 ml. of 1N hydrochloric acid, 10 g. of formalin solution, 900 ml.) there are obtained:

(a) 5.3 g., m.p. 122 - 125° C.; α-compound

(b) 7.0 g., b.p. 124° C./0.4 mm.Hg.; solidifies with ether, in addition 1.2 g. starting amine.

Yield: 70.3% of theory, referred to the reacted ami

EXAMPLE 3

3-methyl-4-(p-methoxyphenyl)-4-hydroxy-piperidine

(a) 62 g. (0.331 mol) of 3-(p-methoxyphenyl)-$\Delta^{3,4}$-pentenonitrile (prepared from 4-methoxypropiophenone and cyanc acetic acid, b.p. 168 - 175° C./12 mm.Hg.) in 500 ml. of methe are mixed with 10 g. of Raney cobalt and 10 ml. of 0.1M ferrou sulphate solution and hydrogenated under pressure at 60 - 70° After separation of the catalyst, the solution is treated with active charcoal and concentrated in a vacuum. The residue is distributed between 200 ml. of 2N hydrochloric acid and benzer the aqueous phase separated and rendered alkaline, while cooli with a concentrated sodium hydroxide solution. The liberated amine is taken up in ether, the extracts dried over potassium carbonate and, after removal of the ether, the residue distill

at water jet pump pressure. The fraction distilling over between 148 and 154° C./12 mm.Hg. consists of 3-(p-methoxyphenyl)-$\Delta^{3,4}$-pentenylamine.

(b) 59 g. (0.309 mol) of this 3-(p-methoxyphenyl)-$\Delta^{3,4}$-pentenylamine are dissolved in 265 ml. of 1.27N hydrochloric acid and 2700 ml. of water (pH 3.0 - 3.5) and mixed with 30.9 g. (0.309 mol) of 30% formalin solution. The reaction mixture is stirred for 78 hours at 88 - 90° C., the neutral parts are removed from the cooled reaction mixture with benzene, the aqueous-acidic solution is clarified with activated charcoal, covered with ether and, while cooling, rendered alkaline with an excess potassium carbonate solution. After separating the organic phase, extraction is carried out three times with ether, the combined extracts are dried over potassium carbonate and the ether is removed in a vacuum. The residue is recrystallized from ethyl acetate. Melting point of the 3-methyl-4-(p-methoxy-phenyl)-4-hydroxy-piperidine: 138 - 141° C.; 15 g.

$C_{13}H_{19}NO_2$ (221.3) Calc. N 6.3

Found N 6.42

After evaporation of the ethyl acetate mother liquor and distillation of the oily residue, there are obtained 10 g. of an oil of b.p. 120 - 126°C./0.05 mm Hg., which crystallizes and is a stereoisomeric mixture of the α and β- form of the above product.

EXAMPLE 4

N,3-dimethyl-4-phenyl-4-hydroxy-piperidine

52.8 g. (0.337 mol) of the 3-phenyl-$\Delta^{3,4}$-pentenyl-amine obtained according to Example 2(a) are dissolved in 345 ml of 1N hydrochloric acid, diluted with 1050 ml. of water and, after the addition of 360 g. (3.6 mol) of 30% formalin solution heated at 80 - 90° C. for about 18 hours; pH: 3 - 4. After cooling, the reaction mixture is rendered alkaline with a 50% potassium carbonate solution and the separated oily base taken up with ether. The residue of the ether solution is dissolved in 200 ml. of methanol, the solution mixed with 36.2 g. of form solution and 3.1 ml. of glacial acetic acid and, after the addition of 10 g. of Raney nickel, hydrogenated at 50 - 60° C. and 50 atmospheres pressure of hydrogen. When the hydrogen absorption is completed, the catalyst is separated, the methanol removed in a vacuum, the residue mixed with water and some potassium carbonate solution, the base taken up with ether and, after evaporation of the ether, distilled; the so obtained N,3-dimethyl-4-phenyl-4-hydroxy-piperidine boils at 125° C./1.5 mm.Hg. to give a rapidly solidifying oil.

Yield 40 g., i.e. 58% of theory. After recrystallization from methyl-cyclohexane: m.p. 116 - 118° C. (β-compound).

$C_{13}H_{19}NO$ (205)

Calc. N 6.82; Found N 6.87

EXAMPLE 5

2-(p-methoxybenzyl)-4-isopropyl-4-hydroxy-piperidine

(a) 177 g. (1.62 mol) of β-isopropyl-allyl cyanide (obtained by condensation of methyl isopropyl ketone with cyan acetic acid; b.p. 62 - 64° C./14 mm.Hg.) are dissolved in 700 of methanol and, after the addition of 20 g. of Raney cobalt a 20 ml. of ferrous sulphate solution, hydrogenated for 2 hours 70° C. After cooling, the catalyst is filtered off with sucti the filtrate clarified with charcoal, filtered and the solvent distilled off at atmospheric pressure. The residue is distill through a column, whereby the resultant mixture of 3-isopropyl $\Delta^{3,4}$-butenylamine, 3,4-dimethyl-$\Delta^{3,4}$-pentenylamine and 3,4-dimethylpentylamine distils over as a colorless liquid at 142 146° C./760 mm.Hg.

(b) 100 g. (0.885 mol) of the mixture obtained acco ing to (a) are dissolved in 840 ml. of 1.15N hydrochloric acid and 4 litres of water (pH 3 - 4). After the addition of 184 g (0.885 mol) of p-methoxyphenyl-glycidic acid methyl ester, the mixture is stirred for 64 hours at 80° C. After allowing to cool, the aqueous acidic solution is decanted off from the smeary material adhering to the wall of the flask, treated wit activated charcoal, filtered and rendered alkaline with excess potassium carbonate solution. After shaking out with ether se times, the extracts are dried over potassium carbonate and con centrated in a vacuum. The 2-(p-methoxybenzyl)-4-isopropyl-4-

hydroxy-piperidine thereby crystallizes out. After recrystalli: from acetone, the melting point is 140 - 142° C.

$C_{16}H_{25}NO_2$ (263.4) Calc. N 5.32 O 12.15

Found N 5.31 O 12.16

When the p-methoxy-phenylglycidic acid methyl ester is replaced by an equimolar amount of benzaldehyde and the procedure is otherwise the same as that described under (b), there is obtained the 2-phenyl-4-isopropyl-4-hydroxy-piperidine of m.p. 138 - 140° C.

$C_{14}H_{21}NO$ (219)

Calc. C 76.67 H 9.65 N 6.38

Found C 76.75 H 9.52 N 6.35

EXAMPLE 6

2-(p-methoxybenzyl)-4-isobutyl-4-hydroxy-piperidine

(a) 150 g. (1.2 mol) of a mixture of 3,5-dimethyl-$\Delta^{2,3}$-hexenonitrile, 3,5-dimethyl-$\Delta^{3,4}$-hexenonitrile and β-isobu allyl cyanide (obtained by the condensation of methyl isobutyl ketone with cyanoacetic acid; b.p. 73 - 75° C./14 mm.Hg.) are dissolved in 500 ml. of methanol, mixed with 15 g. of Raney cobalt and 15 ml. of 0.1M ferrous sulphate solution, and hydrogenated at 70 - 80° C. When the reaction mixture is cold, the catalyst is filtered off with suction, the filtrate decolorized with charcoal, the methanol removed at atmospheric pressure and

the residue distilled in a vacuum. Boiling point of the amine mixture of 3,5-dimethyl-hexylamine, 3,5-dimethyl-$\Delta^{3,4}$-hexenyla and 3-isobutyl-$\Delta^{3,4}$-butenylamine 53 - 58° C./15 mm.Hg.

(b) 80 g. (0.625 mol) of the amine mixture obtained according to (a), 520 ml. of 1.3N hydrochloric acid, 3 litres water (pH of the solution 3 - 4) and 130 g. (0.625 mol) of p-methoxy-phenyl-glycidic acid methyl ester are stirred for 64 hours at 80° C. The cooled solution is decanted, treated with activated charcoal, filtered and rendered alkaline with excess potassium carbonate solution. The liberated base is taken up in ether, the ethereal solution dried over potassium carbonate and evaporated in a vacuum. By vacuum distillation there is obtained from the residue the 2-(p-methoxybenzyl)-4-isobutyl-4-hydroxy-piperidine; b.p. 170 - 180° C./0.3 mm.Hg.; m.p. 120 - 122° C.

$C_{17}H_{27}NO_2$	(277.4)	Calc.	C 73.6	H 9.73	N 5.05
		Found	C 73.9	H 9.62	N 5.04

When, in the above Example, the p-methoxyphenyl-glycidic acid methyl ester is replaced by an equimolar amount of benzaldehyde and the procedure is otherwise the same as that described under (b), there is obtained the 2-phenyl-4-isobutyl-4-hydroxy-piperidine of m.p. 109 - 111° C.

$C_{15}H_{23}NO$ (233)

Calc.	C 77.20	H 9.94	N 6.01
Found	C 77.46	H 9.91	N 5.98

EXAMPLE 7

2-(p-methoxybenzyl)-3-phenyl-4-methyl-4-hydroxy-piperidine

(a) 100 g. (0.636 mol) of a mixture of 3-methyl-4-phenyl-$\Delta^{2,3}$-butenonitrile and 3-methyl-4-phenyl-$\Delta^{3,4}$-butenonitri (obtained by condensation of phenyl-acetone with cyanoacetic acid; b.p. 143 - 146° C./14 mm.Hg.) in 500 ml. of methanol, are after the addition of 12 g. of Raney cobalt and 10 ml. of 0.1M ferrous sulphate solution, hydrogenated for 2 hours at 70° C. After removal of the catalyst, the methanol is distilled off in a vacuum and the residue distilled in a vacuum. The 3-methyl 4-phenyl-butenylamine boils between 126 and 136° C. at a pressur of 15 mm.Hg.

(b) A mixture of 84 g. (0.4 mol) of p-methoxyphenyl-glycidic acid methyl ester, 64.5 g. (0.4 mol) of 3-methyl-4-phenyl-butenylamine, 360 ml. of 1.2N hydrochloric acid and 2 litres of water (pH of the solution 3 - 4) is stirred for 84 hours at 80° C. The aqueous solution is decanted, treated with activated charcoal, filtered, rendered alkaline with a potassium carbonate solution and extracted several times with ether. The combined extracts are dried over potassium carbonate and evaporated in a vacuum. By vacuum distillation of the residue, there is obtained the 2-(p-methoxybenzyl)-3-phenyl-4-methyl-4-hydroxy-piperidine; b.p. 182 - 192° C./0.1 mm.Hg.; m.p. 137 - 139° C.

$C_{20}H_{25}NO_2$ (311.4) Calc. N 4.50 Found N 4.69

EXAMPLE 8

2,3-dimethyl-4-phenyl-4-hydroxy-piperidine

80.5 g. (0.5 mol) of the 3-phenyl-$\Delta^{3,4}$-pentenylamine obtained according to Example 2(a) are dissolved in 525 ml. of 1N hydrochloric acid, diluted with 2000 ml. of water and, after the addition of 24.2 g. of freshly distilled acetaldehyde (0.5 mol), stirred for 40 hours at 80 - 90° C.; pH of the solution: 3 - 4. After cooling, the reaction mixture is rendered alkalir by the addition of a concentrated sodium hydroxide solution, th solution covered with ether and, after mixing at the separating layer, the reaction product separates in crystalline form. After standing, the crystals are filtered off with suction, washed with water and some ether and there is thus obtained a first crystallizate of 22.3 g.; m.p. 170 - 171° C. The residu lye is shaken out several times with ether, and from the combir ether extracts there are obtained an additional 3.8 g.; m.p. 169 - 171° C. After recrystallization from dilute methanol, th 2,3-dimethyl-4-phenyl-4-hydroxy-piperidine obtained has a m.p. of 172 - 173° C.

$C_{13}H_{19}NO$ (205)

Calc.	C 76.05	H 9.33	N 6.82
Found	C 76.00	H 9.36	N 6.78

Upon concentration of the ether solutions, an oil is obtained, which is fractionally distilled; besides 13.7 g. of

starting base, there are obtained 35 g. of a viscous oil of b.p. 125 - 127° C./0.9 mm.Hg., which crystallizes upon trituration with a little ether. Yield: 71.8% of theory, referred to the reacted starting amine.

By the replacement of the acetaldehyde with an equimolar amount of freshly distilled benzaldehyde, there is obtained in analogous manner the compound 2,4-diphenyl-3-methyl-4-hydroxy-piperidine of m.p. 123 - 126° C.

EXAMPLE 9

N,3-dimethyl-4-phenyl-4-hydroxy-piperidine

34.9 g. (0.2 mol) of N-methyl-3-phenyl-$\Delta^{3,4}$-pentenylamine (produced by the N-methylation of the 3-phenyl-$\Delta^{3,4}$-pentenylamine obtained according to Example 2(a); b.p. 108 - 110° C./15 mm.Hg.) are dissolved in 214 ml. of 1N hydrochloric acid, diluted with 780 ml. of water and, after the addition of 21.9 g. of 30% formalin solution, stirred for 40 hours at 80 - 90° C.; pH of the solution ≈3.0. After cooling, the solution is rendered alkaline with sodium hydroxide solution, the base which separates is taken up with ether, separated and the ether evaporated. The solid residue obtained is recrystallized from methyl-cyclohexane, and thus 17.4 g. of the β-form of N,3-dimethyl-4-phenyl-4-hydroxy-piperidine of m.p. 117 - 118° C. are obtained (cf. Example 4).

After evaporation of the solvent there is obtained from the methyl-cyclohexane mother liquor an oil from which, besides 2 g. of starting material, 10.4 g. of a stereoisomeric mixture of the α and β- form of the above product, b.p. 119 - 121°C./1.0 mm Hg. are obtained by distillation. From this mixture there

EXAMPLE 10

N,3-dimethyl-4-phenyl-4-hydroxy-piperidine

a) 31.4 g. (0.24 mole) of 3-phenyl-$\Delta^{3,4}$-pentenonitril (see Example 2a) are dissolved in 500 ml of methanol, and after the addition of 60 g. of glacial acetic acid, 31 g (1 mole) of methylamine and 5 g. of Raney-Ni (or Raney-Co) the mixture is hydrogenated at 60 - 70°C. at a pressure of 50 atmospheres of hydrogen until no more hydrogen is absorb The reaction mixture is allowed to cool, the catalyst is filtered off and the methanol is evaporated in vacuo. The residue is distributed between water and ether, the aqueous phase is separated from the other layer, the former is made alkaline with potassium carbonate and extracted with ether. The two ether extracts are combined, dried over sodium sulf and after the removal of the ether the residue is subjected to fractional distillation. The 1-methylamino-3-phenyl-pentene-(3) boils at 112°/14 Torr.

$C_{12}H_{17}N$ (175.3)

Calculated N 7.99

Found N 7.97

This amine is reacted with formaldehyde in the manner described in Example 2b), whereby a stereoisomeric mixture of the α- and β- form of N,3-dimethyl-4-phenyl-4-hydroxy-piperidine $b.p._{1.5}$ 125°C. is obtained.

b) If in the above process, the methylamine is replac by 107 g. (1 mole) of benzylamine or 121 g. (1 mole) of phenethylamine, the corresponding N-benzyl-3 methyl-4-phenyl 4-hydroxy-piperidine and N-phenethyl-3-methyl 4-phenyl-4-hydroxy-piperidine, respectively, are obtained.

The melting point of the hydrochloride of the N-benzyl compound is 138°C. The melting point of the phenethyl compound in the form of the free base is 106-10

EXAMPLE 11

2-isopropyl-3-methyl-4-phenyl-4-hydroxy-piperidine

60.4 g. (0.375 mol) of 3-phenyl-$\Delta^{3,4}$-pentenylam produced according to Example 2(a), are dissolved in 1800 of water by the addition of 60.7 ml. (0.395 mol) of 6.5N hydrochloric acid and, after the addition of 33 g. (0.458 of freshly distilled isobutyraldehyde, heated at 80-90°C. 144 hours. The pH of the solution is 3.0. After cooling mixing with some ether, the clear solution obtained is re dered alkaline by the addition of a sodium hydroxide solu and the reaction product then separates in crystalline fo After filtering off with suction, washing with water and ether, a first crystallizate of 10.2 g., m.p. 156-157°C., obtained. Upon evaporation of the ether solution and by shaking out the alkaline solution with ether, a second crystallizate of 2 g., m.p. 157°C., is obtained. By dist tion of the residue of the ether solution there is obtain besides 27.2 g. of unreacted starting base, a stereomeric mixture (15.2 g.) boiling at 124 - 129° C./0.4 mm.Hg. from which, by treatment with ether, a further 2.0 g. of

iso
stereomer of m.p. 157° C. can be separated. Yield 27.4 g. of 2-isopropyl-3-methyl-4-phenyl-4-hydroxy-piperidine, i.e. 56.8% of theory, referred to the reacted base. The reaction product consists of at least 51% of the stereomer of m.p. 157° C.

$C_{15}H_{23}NO$ (233)

N Calc. 6.01 Found 6.18

N-methyl derivative m.p. 103 - 104° C.

$C_{16}H_{25}NO$ (247)

Calc. C 77.68 H 10.18 N 5.67

Found C 78.00 H 10.02 N 5.69

12

EXAMPLE ~~11~~

Diethylketone is condensed with cyano acetic acid, the obtained mixture of 90% 1-cyano-2-ethyl-butene-(2), 10% 1-cyano-2-ethyl-butene-(1) Kp_{14} 65 - 68° reduced similarly to Example 1(a) and the reaction product (consisting of 10% of 1-amino-3-ethyl-pentane, 10% 1-amino-3-ethyl-pentene-(2) and 80% 1-amino-3-ethyl-pentene-(3), Kp 152 - 154°) is reacted in the manner described under Example 1(b) with p-methoxyphenylglycidic acid methyl ester, thereby obtaining 2-p-methoxybenzyl-3-methyl-4-ethyl-4-hydroxypiperidine of m.p. 112 - 115° and a mixture of the stereoisomeric form of this compound of $Kp_{0.15}$ 160 - 166°.

$C_{16}H_{25}NO_2$ (263.4) Calc. C 72.8 H 9.48 N 5.32

Found C 72.4 H 9.44 N 5.44

13

EXAMPLE ~~12~~

Methyl-n-propylketone is condensed with cyano acetic acid, the obtained mixture of 1-cyano-2-methyl-pentene-(2), 1-cyano-2-propyl-propene-(2) and 1-cyano-2-methyl-pentene-(1) Kp_{14} 66 - 70° and reacted similarly to Example 1(a) and the reaction product (consisting of 70% of 1-amino-3-methyl-hexene-(3), 15% 1-amino-3-propyl-butene-(3) and 15% 1-amino-3-methyl-hexene-(2) b.p. ~~Kp~~ 148 - 152°) is reacted in the manner described un Example 1(b) with p-methoxyphenylglycidic acid methyl ester, thereby obtaining 2-p-methoxybenzyl-3-ethyl-4-methyl-4-hydroxy-piperidine of b.p. ~~Kp~~ $Kp_{0.2}$ 160 - 168°.

$C_{16}H_{25}NO_2$ (263.4) Calc. N 5.32

Found N 5.40

By replacing the p-methoxyphenylglycidic acid methyl ester with benzaldehyde there is obtained 2-phenyl-3-ethyl-4-methyl-4-hydroxypiperidine, the hydrochloride of which melts at 216 - 218°.

$C_{14}H_{22}ClNO$	(255.8)	Calc.	C 65.7	H 8.60	N 5.47
		Found	C 65.9	H 8.81	N 5.22

14

EXAMPLE ~~13~~

1-Cyano-2,4-diphenyl-butene-(2) (b.p. ~~Kp~~ $Kp_{0.1}$ 156 - 158°) obtained by the condensation of benzylacetophenone and cyano acetic acid is reduced similarly to Example 1(a) and the result

1-amino-3,5-diphenyl-pentene-(3) ($Kp_{0.2}^{b.p.}$ 134 - 138°) is reacted in the manner described under Example 1(b) with formaldehyde, thereby obtaining 3-benzyl-4-phenyl-4-hydroxypiperidine of m.p. 193 - 195°.

$C_{18}H_{21}NO$ (267.3) Calc. N 5.23

Found N 5.08

EXAMPLE 14

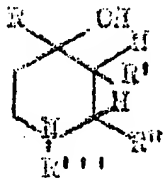
Cyano acetic acid is condensed with 1-phenyl-pentene-(4)-one-(1) [$Kp_{0.1}^{b.p.}$ 87 - 90° produced by the splitting off of the ketone from 2-allyl-2-benzoyl acetic acid ethyl ester ($Kp_{0.2}^{b.p.}$ 118 - 119°)], the resulting 1-cyano-2-phenyl-hexadiene-(2,5) ($Kp_{0.1}^{b.p.}$ 106 - 109°) reduced similarly to Example 1(a) with lithium aluminum hydride to 1-amino-3-phenyl-heptadiene-(3,6) ($Kp_{0.1}^{b.p.}$ 95 - 97°) and this then reacted in the manner described under Example 1(b) with formaldehyde, thereby obtaining 3-allyl-4-phenyl-4-hydroxypiperidine of m.p. 141 - 143°.

$C_{14}H_{19}NO$ (217.3) Calc. N 6.46 O 7.38

Found N 6.30 O 7.42

Claim:

1. 4-Hydroxypiperidine derivatives of the general formula



I

wherein R is an alkyl, aryl, or aralkyl radical, R' is hydrogen, a primary-linked alkyl, alkenyl or aralkyl radical or an aryl radical, R" is hydrogen, an alkyl, alkenyl, aralkyl, aryl or pyridyl radical and R''' is hydrogen, an alkyl or aralkyl radical, the aryl or aralkyl rings are optionally substituted by alkyl, alkoxy, nitro or halogen and the radicals R, R', R''' may be the same or different.

2. 2-p-Methoxybenzyl-3,4-dimethyl-4-hydroxy-piperidine.

3. 2-Phenyl-3,4-dimethyl-4-hydroxy-piperidine.

4. 2-Isopropyl-3,4-dimethyl-4-hydroxy-piperidine.

5. 3-Methyl-4-(p-methoxyphenyl)-4-hydroxy-piperidine.

6. 2-(p-Methoxybenzyl)-4-isopropyl-4-hydroxy-piperidine.

7. 2-Phenyl-4-isopropyl-4-hydroxy-piperidine.

8. 2-(p-Methoxybenzyl)-4-isobutyl-4-hydroxy-piperidine.

9. 2-Phenyl-4-isobutyl-4-hydroxy-piperidine.

10. 2-(p-Methoxybenzyl)-3-phenyl-4-methyl-4-hydroxy-piperidine.

11. 2,3-Dimethyl-4-phenyl-4-hydroxy-piperidine.

12. 2-Isopropyl-3-methyl-4-phenyl-4-hydroxy-piperidine.

13. 3-Methyl-4-phenyl-4-hydroxy-piperidine.

14. 2,4-Diphenyl-3-methyl-4-hydroxy-piperidine.

15. 2-p-methoxybenzyl-3-methyl-4-ethyl-4-hydroxy-piperidine.

16. 2-p-methoxybenzyl-3-ethyl-4-methyl-4-hydroxy-piperidine.

17. 2-Phenyl-3-ethyl-4-methyl-4-hydroxy-piperidine.

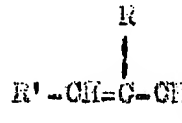
18. 3-Benzyl-4-phenyl-4-hydroxy-piperidine.

19. 3-Allyl-4-phenyl-4-hydroxy-piperidine.

20. N,3-Dimethyl-4-phenyl-4-hydroxy-piperidine.

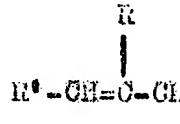
21. 4-Hydroxy-piperidine derivatives of the formula I in Claim 1, substantially as described herein with reference to the Examples.

22. A process for the preparation of 4-hydroxy-piperidine derivatives of formula I in Claim 1 in which R''' is hydrogen which comprises reducing the cyano group of a β,γ-unsaturated nitrile of the formula:



II

to form a γ,δ-unsaturated primary amine of the formula:



III

and condensing the latter in acidic solution, preferably at pH 2 to 4, with an aldehyde R''.CHO; in which formulae R, R' and R'' have the same meaning as in Claim 1.

23. A process for the preparation of compounds of formula I in which R''' is alkyl or aralkyl, wherein a nitril of formula II in Claim 22 is hydrogenated in the presence of

to form a γ,δ-unsaturated secondary amine of formula:

$$R'-CH=\overset{R}{\underset{|}{C}}-CH_2-CH_2NH-R''' \qquad IIIb$$

in which R, R' and R" have the same meanings as in Claim 1 and R''' has the same meaning as above, and the latter is condense in acidic solution with an aldehyde R"CHO.

24. A process according to Claim 22 or 23, wherein the hydrogenation is carried out with catalytically activated hydrogen of average activity in solution in an organic solvent at room temperature or slightly elevated temperatures.

25. A process according to Claim 22 or 23, wherein the condensation of the amine with the aldehyde is carried out at an amine concentration of about 1 - 30%.

26. A process according to Claim 22 or 23, wherein the β,γ-unsaturated nitrile of formula II in Claim 22 used as a starting material contains in admixture the isomeric α,β-unsaturated nitrile of the formula:

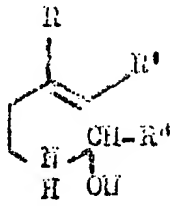
$$R'-CH_2-\overset{R}{\underset{|}{C}}=CH-CN \qquad IV$$

in which R' has the same meaning as in formula II.

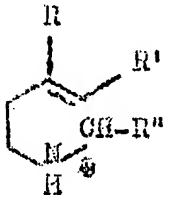
27. A process for the preparation of compounds of formula I in which R''' is alkyl or aralkyl, wherein an amine of the formula IIIa in Claim 22 is subjected to alkylation or aralkylation prior to the condensation with an aldehyde R".CHO.

28. A process for the preparation of compounds of formula I in Claim 1 in which R''' is hydrogen, wherein an amine of

formula IIIa in Claim 22 is reacted with an aldehyde R".CHO to form a compound of the formula:

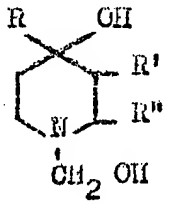


where R, R' and R" have the same meaning as in Claim 1, this compound is hydrogenated and then dehydrated to form a compound:



the latter is subjected to ring closure and simultaneous hydration.

29. A process according to Claim 28, for the preparation of compounds of formula I in Claim 1 in which R''' is methyl wherein the aldehyde R".CHO used for the reaction is formaldehyde, the compound of formula I thus produced, in which R''' is hydrogen, is reacted with an excess of formaldehyde to form the corresponding N-hydroxy compound of the formula:



and the latter is reduced with H_2/Ni.

30. A process for the preparation of compounds of formula I in Claim 1 in which R''' is alkyl or aryl, wherein a compound of formula I in Claim 1 in which R''' is hydrogen is subjected to alkylation or aralkylation.

31. Processes for the preparation of 4-hydroxy-piperidine compounds of the formula I in Claim 1, substantially as described herein with reference to the Examples.

For the Applicants
DR. REINHOLD COHN AND PARTNERS
By:

PC:ea

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